Prostate Cancer: Current Approach and Future Perspective in Castration-resistant Cancer Treatment

Abstract
Prostate carcinoma is one of the most commonly diagnosed solid tumours in males worldwide. Selection of the treatment method is strictly dependent upon disease stage and the patient’s age. Availability of diagnostic tests is constantly increasing in clinical practice, allowing early diagnosis and better chances for complete and permanent recovery. In the case of locally advanced prostate carcinoma, radical surgery or radiotherapy is considered as the most effective therapeutic approach, whereas in metastatic prostate carcinoma, hormone therapy or androgen deprivation therapy (ADT) is the primary therapeutic option. Moreover, increased use of chemotherapy with docetaxel and cabazitaxel in clinical practice has resulted in better prognosis for patients in this advanced stage of the disease.

The biggest challenge for doctors and patients remains the treatment of hormone-resistant carcinoma (which very often is also metastatic). Concerns of today’s medicine regarding effective therapies for this type of disease have recently led to a significant increase in the number of papers/studies on new-generation biological treatments.

Background
Prostate cancer is one of the most common types of cancer among men of all races and usually begins without symptoms.

Early prostate cancer may not cause any symptoms for years, therefore screening for prostate cancer is recommended, especially in high-risk populations. Recently, due to better availability of diagnostic tests, particularly determination of serum prostate specific antigen (PSA), the detection rate of prostate carcinoma has significantly improved. Blood PSA levels above 4 ng/ml may suggest the presence of carcinoma cells and indicate the need for further diagnostics. However, studies have indicated that PSA levels below 4 ng/ml are not definitely predictive of the absence of prostate carcinoma.

Most cases of prostate carcinoma (90%) are adenocarcinomas, malignant tumours of the epithelial tissue. Histopathologic differentiation is based on the Gleason score\(^3\), a combined total of the two most prevalent patterns in the biopsy material (Table 1).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Histopathological characterisics</th>
<th>15-year risk of death due to prostate carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>Well differentiated</td>
<td>4-7%</td>
</tr>
<tr>
<td>5</td>
<td>Well differentiated</td>
<td>6-11%</td>
</tr>
<tr>
<td>6</td>
<td>Well differentiated</td>
<td>18-30%</td>
</tr>
<tr>
<td>7</td>
<td>Moderately differentiated</td>
<td>42-70%</td>
</tr>
<tr>
<td>8-10</td>
<td>Poorly differentiated</td>
<td>60-87%</td>
</tr>
</tbody>
</table>

The prevalence of prostate cancer in Europe was estimated at 416,700 cases in 2012\(^1\). Prostate cancer has been recognised as the third leading cause of death in Europe. According to the International Agency for Research on Cancer, the biggest incidence of prostate cancer in 2012 was reported in northern European countries (Norway, Sweden, Ireland, Iceland and Switzerland). Reported mortality was also the highest in Scandinavian countries. Based on data analysed by the American Cancer Society, it is estimated that in the US about 220,800 new cases of prostate cancer will be diagnosed in 2015, and the number of deaths will reach 27,540.

One of the primary risk factors is age. Prostate carcinoma is usually diagnosed in patients aged over 65. According to the American Cancer Society, about six in 10 cases of prostate cancer are diagnosed in men over 65. Other risk factors include genetic burden and race (prostate cancer prevalence is highest among African and Caucasian men).

Prostate carcinoma is most commonly located in the peripheral zone and typically multifocal. The term advanced prostate carcinoma is used to describe the stage of the disease in which the tumour has already spread beyond the organ and infiltrated the surrounding tissues and organs (locally advanced carcinoma) or has metastasised to bones or distant organs (disseminated, metastatic cancer).

Early detection significantly increases the chances of
survival. In the United States, where screening tests are commonly used, over 90% of prostate cancer cases are diagnosed in the organ-limited or locally advanced stage, and five-year survival rate at this stage is nearly 100%.

According to the most recent data analysed by the American Cancer Society (including all stages of prostate cancer) the survival rates are as follows:

- The relative five-year survival rate is almost 100%
- The relative 10-year survival rate is 99%

### Therapy – General Principles

Prostate cancer growth is androgen-dependent, therefore androgen blockade is an effective anti-cancer therapy. It can be achieved with surgical castration, radiation therapy, or medical castration (hormone therapy).

The choice of the therapy course largely depends on the stage of the disease. General therapeutic approaches in prostate carcinoma are outlined in Table 2.

#### Table 2. Prostate carcinoma treatment options

<table>
<thead>
<tr>
<th>Organ-limited prostate carcinoma</th>
<th>Locally advanced prostate carcinoma</th>
<th>Metastatic prostate carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• radical prostatectomy</td>
<td>• radical radiotherapy</td>
<td>• palliative hormone therapy</td>
</tr>
<tr>
<td>• radical radiotherapy</td>
<td>• hormone therapy</td>
<td>• palliative radiotherapy</td>
</tr>
<tr>
<td>• radical brachytherapy</td>
<td></td>
<td>• palliative brachytherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• novel drugs</td>
</tr>
</tbody>
</table>

#### Table 3. Hormonal therapies in prostate carcinoma

<table>
<thead>
<tr>
<th>Gonadotropin analogues</th>
<th>Gonadotropin antagonists</th>
<th>Antiandrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Goserelin</td>
<td>• Degarelix</td>
<td>• Flutamide</td>
</tr>
<tr>
<td>• Leuprolelin</td>
<td></td>
<td>• Bicalutamide</td>
</tr>
<tr>
<td>• Triptorelin</td>
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</tbody>
</table>

#### Table 4. Definition of castration-resistant prostate carcinoma. PSA – prostate specific antigen, RECIST - Response Evaluation Criteria in Solid Tumors

<table>
<thead>
<tr>
<th>Biochemical progression</th>
<th>Radiographic progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castrate level of blood testosterone (&lt; 50 ng/dl or 1.7 nmol/l)</td>
<td>Castrate level of blood testosterone (&lt; 50 ng/dl or 1.7 nmol/l)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Three consecutive PSA increments within 1 week by 50% from the lowest PSA level</td>
<td>• development of min. 2 bone lesions</td>
</tr>
<tr>
<td></td>
<td>• or development or growth of metastatic lesions in soft tissues, according to RECIST</td>
</tr>
</tbody>
</table>

- The relative 15-year survival rate is 94%

**Therapy – General Principles**

Prostate cancer growth is androgen-dependent, therefore androgen blockade is an effective anti-cancer therapy. It can be achieved with surgical castration, radiation therapy, or medical castration (hormone therapy).

The choice of the therapy course largely depends on the stage of the disease. General therapeutic approaches in prostate carcinoma are outlined in Table 2.

#### Radical surgery

Radical surgery is indicated only in patients with prostate-limited carcinoma (cT1-2 N0 M0) whose life expectancy is above 10 years.

#### Radical irradiation – teletherapy and/or brachytherapy

Radical irradiation – teletherapy and/or brachytherapy is also indicated in patients with prostate-limited carcinoma (stage cT1-T3 N0 M0) and some cases of locally advanced carcinoma (T4 and N(+)).

#### Hormonal therapy (HTH) or androgen deprivation therapy (ADT)

Hormonal therapy (HTH) or androgen deprivation therapy (ADT) is the primary therapy for advanced disease. The treatment eliminates the endogenous androgens in patients who are not eligible for radical therapy. Hormonal therapy is the first-line treatment for advanced prostate cancer. This course of treatment allows slowing down the cancer growth but it does not cure the disease itself.

Traditional ADT (Table 3) includes a variety of approaches:

- surgical castration – removal of the testes, thus blocking the secretion of androgens;
- pharmacological castration – blocking the secretion of androgens at the pituitary level;
- intracellular pharmacologic castration – blocking the
Effect of androgens on prostate cells with androgen receptor blocking drugs (so-called anti-androgens).

Combination of surgical and pharmacologic castration is known as total or maximal androgen blockade (MAB). Ablation therapy results in reducing testosterone levels to castration values, i.e. <50 ng/ml.

**Hormone Resistance**

Unfortunately, in many cases, the prostate carcinoma progresses despite castration and very low blood testosterone levels. Despite the high efficacy of hormonal therapy, cancer cells become adapted to low (castrate) androgen levels after some time and castration-resistant prostate cancer (CRPC) develops. The definition of CRPC is presented in Table 4.

Typically the skeletal system is the first area of metastasis for prostate carcinoma. Bone metastases are observed in 90% of patients with metastatic castration-resistant prostate carcinoma (mCRPC). This patient population requires particular and thorough therapy due to severe disease symptoms, dramatically affecting the quality of life. The objective of therapy is to improve quality of life, but also prolong time to progression and total survival. Further efforts are being made to modify early-stage treatment to obtain maximum improvement of time to development of hormone-resistance and metastases. How to proceed, if an aggressive type of disease is suspected, particularly in young patients with high histologic grade (Gleason 8 or above), remains one of the most challenging questions.

Despite insufficient knowledge of the precise mechanisms involved in the development of CRPC, difficulties and challenges related to CRPC therapy have led to the development and launch of several new drugs, improving patients’ prognosis. These new medicines include: abiraterone, enzalutamide, sipuleucel, docetaxel (new in this indication), and cabazitaxel (Diagram 1).

**Chemotherapy**

For many years prostate cancer has been believed to be cytostatic-resistant. A significant step forward was made in 2004, with the publication of two large studies comparing

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**Table 1. Therapeutic options for patients after biochemical progression (increase of PSA level) used in combination with hormonal therapy**

**Table 2. Selected randomized phase 3 clinical trials in patients with known castration-resistant prostate cancer: PSA regression rate, pain, total survival, time to progression. EMP = estramustine; HC = hydrocortisone; 1p<0.000 compared to mitoxantrone; 2p<0.001 compared to mitoxantrone**

**Table 3. Selected randomized phase 3 clinical trials in patients with mCRPC:**

**Table 4. Definition of CRPC**

**Table 5. Selected phase 3 clinical trials in patients with known castration-resistant prostate carcinoma:**

**Table 6. Selected randomized phase 3 clinical trials in patients with known castration-resistant prostate cancer**

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**Diagram 1. Therapeutic options for patients after biochemical progression (increase of PSA level) used in combination with hormonal therapy**

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the efficacy of docetaxel and mitoxantrone plus prednisone chemotherapy, which was the standard therapy at that time. Docetaxel is an anti-cancer drug that works by binding to microtubules and stabilising them, which eventually leads to cell death. The safety and efficacy of docetaxel in combination with prednisone and prednisolone in patients with hormone-independent prostate carcinoma has also been studied in a multi-centre Phase III randomised trial TAX 327. This study recruited 1006 patients. The median (mean) survival time was 18.9 months compared to 16.6 months in 327. This study recruited 1006 patients. The median (mean) survival time was 18.9 months compared to 16.6 months in the mitoxantrone group (HR=0.7695 %, CI: 17.0-21.2) \(^{9,12}\). The only drug which has shown an improvement of total survival in patients with progression following docetaxel-based chemotherapy was cabazitaxel. This semi-synthetic taxoid belongs to new generation antineoplastic drugs and is characterised by partial lack of cross-resistance to docetaxel. The TROPIC study comparing treatment with cabazitaxel and prednisone vs. mitoxantrone and prednisone has shown improvement of median survival time by more than two months (15.1 vs. 12.7 months, respectively) and a doubled median time to progression (2.8 vs. 1.4 months)\(^{13,16}\).

### Current Hormonal Therapy in Advanced Prostate Carcinoma

Recently, two novel hormone therapies have been introduced based on abiraterone and enzalutamide. They act by blocking androgen receptor activation pathways, but their mechanism of action is different than in therapies used so far.

Therapeutic benefits of abiraterone and enzalutamide have been evaluated following docetaxel chemotherapy, as well as prior to docetaxel chemotherapy as a first-line therapy in patients diagnosed with CRPC. Results of selected Phase III clinical trials are presented in Table 6.

Abiraterone selectively inhibits CYP17 activity (17α-hydroxylase and C17,20-lipase activity). This enzyme is responsible for the biosynthesis of androgens in the testes, adrenal glands and prostate cancer tissue. Blocking its activity results in stopping testosterone production. In a prospective, placebo-controlled Phase III randomised clinical trial (COU-AA-301) abiraterone was used in combination with prednisone in patients with known castration-resistant prostate cancer, following a failure of docetaxel therapy. A statistically significant therapeutic benefit was shown – mean total survival in the non-abiraterone group was 11.2 months (95% CI 10.4-13.1 months) vs 15.8 months (95% CI 14.8-17.0 months) in the abiraterone arm. Median follow-up time was 20.2 months. The study also demonstrated increased median time to PSA progression of 8.5 months (95% CI 8.3-11.1) vs 6.6 months (95% CI 5.6-8.3); HR 0.63; p< 0.0001.

In another prospective Phase III randomised clinical trial (COU-AA-302) abiraterone was used in combination with prednisone in docetaxel-naive patients with known castration-resistant prostate carcinoma. The study demonstrated an increased median of total survival by 4.8 months (35.3 vs 30.1 months; HR 0.79, p=0.0151). Abiraterone also reduced the risk of radiographic progression (rPFS, radiographic progression free survival) or death by 47% compared to placebo (HR=0.530; 95% CI: 0.451; 0.623; p<0.0001)\(^{6,8}\).

Enzalutamide is indicated for the treatment of metastatic castration-resistant prostate cancer in patients with disease progression during or following docetaxel treatment. It is a potent inhibitor of the androgen receptor signalling pathway. It blocks several stages of the androgen receptor signalling pathway. The efficacy and safety of this drug have been evaluated e.g. in a randomised, placebo-controlled, multi-centre Phase III clinical trial in patients with metastatic castration-resistant prostate carcinoma, following earlier docetaxel therapy. The patients received a concomitant gonadotropin-releasing hormone (GnRH) analogue or underwent surgical castration (orchectomy). Progression free survival confirmed by radiologic evaluation determined with RECIST (Response Evaluation Criteria In Solid Tumors) v. 1.1 criteria was 8.3 months in the enzalutamide group and 2.9 months in the placebo group (HR = 0.404, 95% CI: [0.350; 0.466]); p < 0.0001).

Combination therapies including both products (enzalutamide and abiraterone) are currently under investigation in mCRPC. These medicinal products with different targets given in parallel may demonstrate significantly higher efficacy than when used alone.

### Immunotherapy for Prostate Carcinoma

The purpose of immunotherapy is to induce and stimulate immunologic mechanisms in order to destroy cancer cells. A breakthrough strategy in the treatment of CRPC turned out to be the use of autologous dendritic cells, professional antigen presenting cells. Sipuleucel-T is a vaccine for personalised presenting cells. Sipuleucel-T was developed based on autologous dendritic cells, professional antigen presenting cells. The purpose of immunotherapy is to induce and stimulate immunologic mechanisms in order to destroy cancer cells. A breakthrough strategy in the treatment of CRPC turned out to be the use of autologous dendritic cells, professional antigen presenting cells. Sipuleucel-T is a vaccine for personalised

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**Table 7. Selected clinical trials of Sipuleucel-T**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study drug (sample size)</th>
<th>Time to progression (months)</th>
<th>Total survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantoff</td>
<td>2010</td>
<td>Sipuleucel-T (341) vs placebo (171)</td>
<td>3.7 vs. 3.6</td>
<td>25.8 vs 21.7 months (p&lt;0.03)</td>
</tr>
<tr>
<td>Small</td>
<td>2006</td>
<td>Sipuleucel-T (82) vs Placebo (45)</td>
<td>11.7 vs. 10</td>
<td>25.9 vs 21.4 months (p&lt;0.03)</td>
</tr>
</tbody>
</table>
future prognosis in patients with CRPC. Further studies, both in the field of immunology and cancer molecular biology, should allow the identification of currently unknown therapeutic targets, and design new, promising systemic treatment strategies of early and advanced prostate cancer. Results of selected clinical trials are presented in Table 7. Sipuleucel-T was approved by the FDA in 2010 and shortly after the marketing authorization, the National Comprehensive Cancer Network added Sipuleucel-T as a category 1 recommendation for patients with castration-resistant prostate cancer.

Summary and Conclusions

Prostate cancer is one of the most common types of cancer and one of the leading causes of cancer death worldwide. The most difficult type of prostate cancer for effective therapy is metastatic castration-resistant prostate cancer. CRPC remains an incurable disease usually associated with poor prognosis and short survival time. A multidisciplinary approach is advised in the treatment of patients with a known castration-resistant stage of prostate carcinoma, but patient care remains a tremendous challenge for today’s medicine. Very high incidence of prostate cancer and lack of fully effective treatment methods of its advanced, castration-resistant forms have resulted in a dynamic progress of clinical trials of novel therapies. The primary purpose of novel therapies, including chemotherapies, is to reduce the patient’s pain, improve quality of life and above all improve survival rates. Positive and promising study results have been obtained for abiraterone, enzalutamide as well as for Sipuleucel-T. During the last years these products were granted marketing authorisation both in the United States (FDA) and throughout the European Union (EMA), however because of the high cost of novel therapies, patients’ access to advanced treatment is still limited in many countries.

Currently, the potential use of these hormonal drugs is also being studied in other clinical indications, e.g. the use of enzalutamide prior to radical prostatectomy. Therapies targeting the receptors and signalling pathways in prostate carcinoma cells and endothelium provide a true opportunity for improving future prognosis in patients with CRPC. Further studies both in the field of immunology and cancer molecular biology should allow the identification of currently unknown therapeutic targets, and design new, promising systemic treatment strategies of both early and advanced prostate cancer.

References


Bożena Sikora-Kupis is an experienced oncologist with over 10 years of practice in the clinical research area as an investigator and medical monitor. With the broad scientific background and high-level education gained with the medical doctor degree and additional postgraduate diploma of specialty of oncology she has comprehensive knowledge of the industry. She practiced in the department of diagnostic oncology in the Institute of Oncology, Warsaw, Poland, with a focus on prostate cancer. At KCR she currently supports Medical Affairs Team with her extensive hands-on experience in managing clinical studies in complex indications.

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